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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,271	04/12/2001	William Widner	5455.210-US	4969

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EXAMINER	
MONSHIPOURI, MARYAM	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,271	WIDNER ET AL.	
	Examiner	Art Unit	
	Maryam Monshipouri	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *79 and 81* is/are allowed.

6)☒ Claim(s) *74-78,80 and 82-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A **request for continued examination** (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/28/2005 **has been entered**.

DEATLED ACTION

Claims 1-73 are canceled. Claims 74-93 are under examination on the merits. Applicants' arguments filed on 2/28/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority Data

USPTO internal records refers to patent case serial No. 09/256,377 filed 2/24/1999, now abandoned, which appears to be a Continuation In Part of case serial No. 09/031,442, filed 2/26/1998 which is now U.S. Patent No. 5,955,310. However, the former case has a totally different title than this invention. Applicant is advised to clarify the priority data of the instant case in response to this office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 74-77, 80, 82-84, 86-93 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hung (Mol. Gen. Genet., 219, 129-136, 1989, cited previously), in view of Lereclus (WO 94/25612, cited previously). In traversal of this rejection applicant amended the base claim 74 and basically provides the same arguments addressed previously. Briefly applicant continues to argue that Figure 5 of Lereclus demonstrates low levels of lacZ expression in a strain harboring pHT901'lacZ which has the cryIIIa downstream region situated downstream of lacZ promoter. Further, even though in Figure 6, Lereclus shows that pHT7902'lacZ construct (where the cryIIIA promoter is upstream of the cryIIIA "downstream region" which is upstream of the lacZ gene) increases expression of the lacZ gene relative to the pHT7901'lacZ construct, no evidence is presented that cryIIIA region can be used with other promoters that are foreign to the cryIIIA "Downstream region" to increase gene expression. In fact, based on the results of Lereclus et al., the cryIIIA "downstream region" appears to be specific to the cryIIIA promoter.

Applicant further indicates that the references cited by the examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejection of the present claims. Moreover, in view of applicant, there is no motivation to inserting the "downstream region" of Lereclus into the DNA construct of Hung because there is no reasonable expectation of success of increasing expression of a gene based on the results obtained by Lereclus wherein the mRNA processing /stabilizing sequence is foreign to the "consensus" promoter.

Hence, in view of the above arguments applicant request withdrawal of the rejection.

These arguments were fully considered but were found **unpersuasive.** This is because it appears that applicant may have misunderstood the data presented in Figures 5-6 of Lereclus patent. Applicant is respectfully requested to read column 12 of said U.S. Patent wherein the details of plasmids construction are discussed. Based on the details provided both pHT304'lacZ and pHT7901'lacZ lack promoters. Thus, in the latter construct even though the "downstream region" is present, said region could not enhance lacZ expression because it can only act in the presence of a promoter. In figure 6, once a promoter, which in this case happens to be a cryIIIa promoter, is present together with the "downstream region" , the lacZ expression is significantly enhanced. Hence, Figure 5 of Lereclus **does not** provide negative effects of placing "downstream region" downstream of lacZ promoter, on lacZ expression.

Further, as already explained in the office action dated 10/6/2004, in column 2 of U.S. Patent No. 6,140,104 (which has been cited by applicant as U.S. equivalent of Lereclus French patent WO 94/25612) Lereclus clearly indicates that the promoter from his constructs may be both endogenous or exogenous to the host used so long as it is functional. In column 5 Lereclus specifically teaches some examples of exogenous promoters which may be used in his plasmid constructs including lacZ promoter, which inherently originates from E. coli.

Therefore, the examiner does not find any reason as to why Hung in view of Lereclus could not be combined, according to previous office actions to render the

present invention obvious. Further, based on the teachings of Lereclus inserting the " downstream region" upstream of the promoter that is upstream of the lacZ gene is reasonably expected to enhance gene expression in a Bacillus host, wherein the promoter can be either exogenous or exogenous.

Claims 89-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung (cited previously) in view of Lereclus (cited previously) further in view of Jorgensen (cited previously).

As stated above, Hung in view of Lereclus teaches a Bacillus cell comprising an extra chromosomal DNA construct comprising a consensus promoter having a sequence TTGACA for the "-35" region and TATAAT for the "-10" region operably linked to a single copy of a reductase encoding gene or CryIIIa gene and an mRNA processing/stabilizing sequence located downstream of the consensus promoter and upstream of said reductase encoding or CryIIIa gene. Hung in view of Lereclus does not teach a Bacillus cell wherein said promoter/gene/mRNA stabilizing construct is contained in the chromosome of the Bacillus cell.

Jorgensen in pages 14-15 teach construction and transfer of a Bacillus licheniformis promoter and a DNA construct comprising said promoter and genes encoding enzymes such as alpha-amylase, protease or glycosyl transferase (see claim 10) into the chromosome of a Bacillus host cell (see the list of Bacillus host cells in claim 15).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to start with the Bacillus host cell of Hung in view of Lereclus and

use the genes (such as amylase or protease encoding genes) and methods of Jorgensen in order to incorporate said construct into the chromosome of the Bacillus cell.

One of ordinary skill in the art has a reasonable expectation of success in integrating either of the above mentioned DNA constructs into the chromosome of Bacillus host cell according to Jorgensen because methods of chromosomal integration of genes in Bacillus and E. coli are well established in the prior art, as evidenced by the disclosure of Jorgensen, rendering the invention obvious.

In traversal of this rejection applicant relies on the same arguments discussed in traversal of Hung in view of Lereclus addressed above. Therefore the rejection is maintained for the response provided above in addition to explanations provided in the previous office actions.

Claims 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung (cited previously) in view of Lereclus (cited previously) further in view of Diderichsen (Res. Microbiol., 142, 7-8, 793-96, 1991). As stated above, Hung in view of Lereclus teaches a Bacillus cells comprising a DNA construct comprising a consensus promoter having a sequence TTGACA for the –"35" region and TATAAT for the "-10" region operably linked to a single copy of an alpha amylase gene and an mRNA processing/stabilizing sequence located downstream of the consensus promoter and upstream of said amylase encoding gene. Hung in view of Lereclus does not teach a Bacillus cell comprising a construct wherein the "consensus" promoter is obtained from amyQ.

Diderichsen teaches using amyQ and amyM promoters in enhancing expression of stearothermophilus alpha amylase (amyS) gene in Bacillus subtillis and displays 3-fold increase in amyS productivity compared to an equivalent B. Subtillis construction (see abstract).

At the time the invention was made it would have been obvious to one of ordinary skill in the art to start with the Bacillus host harboring the construct of Hung in view of Lereclus and replace the promoter of said construct with that of Diderichsen in order to enhance expressing of any exogenous enzyme expressing gene including the alpha-amylase of Diderichsen. One of ordinary skill in the art is motivated in expressing amyS of Diderichsen at high quantities using amyQ promoter of Diderichsen in the construct and Bacillus of Hung in view of Lereclus because Diderichsen specifically teaches that thermostable alpha amylase is used for industrial production of glucose or high fructose syrups in food industry.

Finally, one of ordinary skill in the art has a reasonable of expectation of success in expressing high levels of alpha amylase because Lereclus teaches that amylase promoters may be successfully used in its constructs (see column 5 of U.S. Patent 6,140,104) and Diderichsen displays positive results when amyQ promoters were used in expression of amyS in B. substillis host cells rendering the invention obvious.

Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hung (cited previously) in view of Lereclus (cited previously) further in view of Jogensen* (WO 96/23073, 8/1996). As explained previously, Hung in view of Lereclus teaches a Bacillus cells comprising a DNA construct comprising a consensus promoter having a sequence

TTGACA for the –"35" region and TATAAT for the "-10" region operably linked to a single copy of an alpha amylase gene and an mRNA processing/stabilizing sequence located downstream of the consensus promoter and upstream of said amylase encoding gene. Hung in view of Lereclus does not teach a Bacillus cell which contains no selectable marker gene.

Jogensen* (see abstract and page 1) teaches preparation of a DNA construct useful for the construction of a bacterial cell (more specifically a bacillus cell) having integrated more than one copy of a DNA sequence of interest into its genome. Which cell may be free of any selection markers and a method of construction of such cells.

At the time the invention was made it would have been obvious to one of ordinary skill in the art to start with the Bacillus cell of Hung in view of Lereclus and delete the selectable markers of the construct comprised therein, according to Jorgensen* such that plasmids of said Bacillus may be used for homologous recombination into chromosome of sad Bacillus or other species of Bacillus family.

One of ordinary skill in the art would be motivated to delete selectable marker genes of such plasmid comprised in Bacillus of Hung in view of Lereclus according to Jergensen* because Jergensen* teaches that the presence of such marker genes in chromosome of a Bacillus host cell are undesirable from an a environmental and product approval point of view (see page 4).

Finally, one of ordinary skill in the art has a reasonable expectation of success in preparing such Bacillus host because Jergensen* has successfully prepared and claimed (see claim 30) such cell prior to this invention rendering the invention obvious.

Allowable subject matter

Claims 79, and 81 are allowed for the reasons of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maryam Monshipouri whose telephone number is (571) 272-0932. The examiner can normally be reached on 7:00 a.m to 4:30 p.m. except for alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnanthapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maryam Monshipouri Ph.D.

Primary Examiner